THE VENOM APPARATUS OF THE STONE FISH (*Synanceja horrida*).

By J. V. Duhig, M.B., Director, and Gwen Jones, Histologist,
Brisbane and District Laboratory, Hospital for Sick Children, Brisbane.

(Text-figures 1-8.)

A considerable amount of work has been done on the secretory activity of the skin-glands of fishes. Most of the work, however, is morphological and descriptive, and remarkably little observation has been made of the function of these glands, and still less of the effect of their secretion.

Of all the works consulted, that of Reed[1] is in its way the most complete. He has made a very careful study of the histology and development of the dermal glands of a large number of species of fishes reputed to be poisonous. He provides also a very complete bibliography, and his paper is a masterly summary of the subject. To this paper a good deal of reference will further be made.

Citterio[2] gives an excellent morphological study of *Ameirurus catus*, and the authors of this paper in general confirm his histological findings.

Muir Evans[3] traverses the literature dealing with the defensive spines of fishes, and gives some observations on the nature of the venom apparatus of *Trygon pastinaca*, *Acanthius vulgaris* (spiny dog-fish), *Cestracion philippi* (Port Jackson shark), and *Chimæra monstrosa*. He says, "In this country very little original work has been done on the subject of defensive spines of fish." He notes that down to the time of Cuvier little evidence existed that fish secreted a poison. The naturalists up to that time believed that the lesions produced by fish-spines were traumatic rather than toxic. Alman (1841) then "described a gland at the root of the spine of the lesser Weever. His discoveries were widened and confirmed by Byerley, Gunther, Bottard, and others" (Evans).

Bottard[4] (1889) described the poison apparatus of *Synanceia* (*sic*), but as his paper is inaccessible we have no means of knowing whether he actually confirmed by experiment his assumption that the dorsal spines he described secreted a poison.

Gunther in his book devotes a few lines to *Synanceja*, and accurately figures the poison gland of the dorsal spines, though later Starr Jordan makes the mistake of surmising that the poison gland of this species is to be found at the base of the spine.

The following paper is a preliminary study dealing with the osteology, myology, and histology of the venom apparatus of the dorsal spines, along with some observations on the toxicology of their secretion. Abundant evidence is brought to show that the sacs lying along these spines do secrete a substance which is highly toxic to laboratory animals.

Stimulated by Reed's work, a histological study was also made of certain skin organs likely to be incriminated as venom producers. Histological study was made of certain portions of the skin, the results of which are similar to those obtained by Reed, but this part of the work is far from complete from the toxicological aspect, and it is hoped to supplement it at a later date. [We have since shown that the secretion of the broad tubercles differs from that of the dorsal spine sacs.]

The reason for this is that (i) it is difficult to obtain living material, (ii) it is more difficult still to obtain sufficient skin secretion under laboratory conditions to produce experimental effects, though it will be shown that there is a probability that this difficulty is more apparent than real.

The present study deals, therefore, primarily with the sacs of the *dorsal* spines of *Synanceja horrida,* and for the first time certain physiological and serological findings are produced in support of the view that these sacs secrete a poison. The purely descriptive parts of this paper were worked up from two specimens supplied by Mr. H. A. Longman, Director of the Queensland Museum, and the toxicology from a specimen supplied by Dr. F. G. Power, by courtesy of the master of the s.s. "Bombala."

Description.—Macroscopic:—The measurements of the four specimens examined are:—

Reference.	Length.	Head.	Tail.	Height.
	cm.	cm.	cm.	cm.
Q.M. I/2217	30	8	5	9
Q.M. I/1193	24	7·5	4	8
B.L. F/I	24	7	4	8·5
B.L. F/II	34	11	5·5	..

B.L.F/II showed certain marked variations from other specimens examined. See Appendix.

In all specimens the dorsal fin consists of 14 spines, 13 of which can project beyond the enveloping skin, and one, that between the tail and the next spine cranially, is completely enveloped by skin, and apparently unable to exert any defensive function.

Thirteen spines therefore, though normally well covered with skin, can readily be exposed along a short portion of their length. Reed remarks (*loc. cit.*): "In the Scorpenidæ and others the spines are naked in the distal portion and are so related to the gland and surrounding integument that there is formed a mobile sheath, which easily slips away from the apex of the spine. . . . Thus the spine is not only free and inflicts a wound without injury to itself or surrounding tissues, but is freely supplied with venom. Such an apparatus is probably to be construed as none other than a defensive device." This is exactly the opposite to the condition common to the catfish, in which the spines are so completely covered with integument "that when inflicting a wound it is necessary for the spine to first puncture the skin which covers it."

The skin of the stone fish, though covering the spines, has no attachment to them above 0·5 cm. from the tip. From a point 0·5 cm. from the tip of the spine to within about one quarter of the length of the spine from the articulation with the interneurals, the skin is attached to the spine. The attachment of the skin is very firm and fibrous, lying in shallow grooves on either side of the spine until just above the articulation with the interneurals, where the attachment is complete all round the spine.

On dissection we found a muscle in the superficial fascia, fibres of which ended dorsally along the spines at the junction of the middle and distal thirds of the spine. This muscle was traced to an origin on the occipital region of the skull where it is 3 cm. broad in average specimens. From there it extends along the dorsum, keeping the same width until on either side it reaches a point opposite the 12th spine, where it spreads out fanwise to be inserted into the dense fascia about the base of the anal fin.

This muscle is evidently for the purpose of retracting the skin over the spines—"a *panniculus spinæ.*" It has no connection with the intrinsic muscles of the vertebral column, since its fibres run at right angles to them.

Dissected from their skin attachments, we find that the spines are loosely articulated with the interneurals.

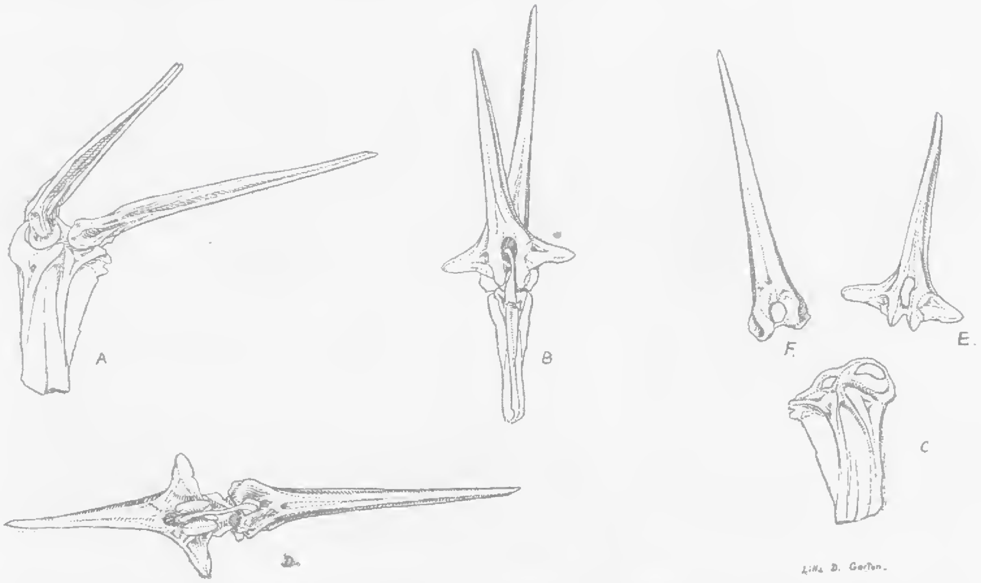
In specimen Q.M.I/1193, we found the spines to measure as follows (measured from tip to articular surface):—

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.	XIII.	XIV.
Centimetres	2·25	3·25	3	2·5	2·7	2·8	2·8	2·8	2·9	3	2·8	3	3·3	3·6

With the exception of the first, all the spines are of the same form—at the articular end fairly expanded into lateral condyles and tapering to a fine point at the distal end. Between the condyles the bone is perforated for the purpose of articulating with a ring on the interneurals. Along the lateral aspects of the spines are shallow grooves continuing almost to the tip. The first spine has greatly extended condyles which end laterally in a rather sharp point. (Fig. I, E, 1st spine; F, 2nd spine.)

The spines articulate with the interneurals by a semicircle of bone on the dorsal aspect of the interneural passing through the perforation of the spine between the condyles. (Fig. I, A, lateral aspect; B, cranial aspect; D, dorsal aspect.)

The first and second interneurals are fused, all others are separate. Each interneural is roughly rectangular or rhomboidal in shape, and along the lateral aspect of each is a median ridge. (Fig. I, C and A.)

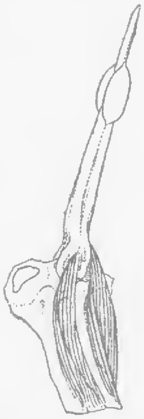


Text-figure 1.—1st and 2nd dorsal spines of *Synanceja horrida* and their articulation with interneurals.

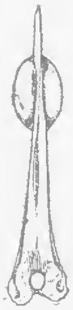
Along the interneurals laterally run two muscles, one cranial and one caudal, to the median lateral ridge. The lateral muscle cranial to the ridge arises on the ventral and cranial aspect of the condyle of the spine, while that caudal to the median ridge arises from the dorsal and caudal aspect of the lateral condyle. Both muscles are inserted into the edges of the interneural and the median ridge. A diagram of the musculature is shown in Fig. II. The muscle placed cranially elevates the spine, that caudally depresses it; named for convenience "*Levator spinæ*" and "*Depressor spinæ*" respectively.

Careful dissection of the soft tissues about the spine will reveal two sacs, one on either side of the spines, brownish in colour in preserved, pearly white in fresh specimens. (See Figs. II and III.) These sacs vary a little in size but well developed they measure, both together, about 0·5 cm. across, each being about 1 cm. long, extending down the lateral grooves of the spine from within about 0·5 cm. to 0·7 cm. of the tip to 1·5 cm. to 1·7 cm. down the spine. A duct, very tiny but visible through a hand lens, runs from the sacs along the lateral grooves towards the tip of the spines where it is lost to view.

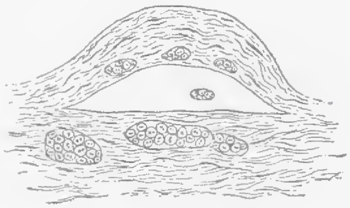
The spines do not always bear uniformly well-developed sacs. In all three specimens examined the sacs in a few instances were reduced to mere vestiges. In specimen Q.M.I/2217 the sacs of the 2nd spine were vestigial; there were no sacs on the 4th, but those of all other spines were well developed. [Specimen B.L/F.II had no sacs at all—see Appendix.] The microscopic structure of the sacs has been studied in serial sections and will be described later.



Text-figure 2.—Diagram of levator and depressor muscles of spine.



Text-figure 3.—Poison sac of *Synanceja horrida*.



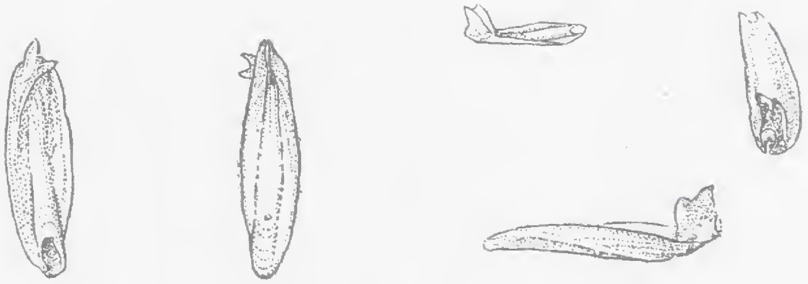
Text-figure 4.—Diagram of histology of "Broad tubercle."

OTHER SKIN GLANDS LIKELY TO BE INCRIMINATED AS VENOM SECRETORS.

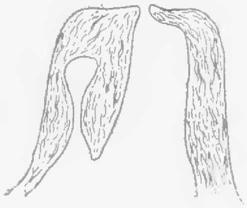
Tubercles.—*Synanceja horrida* is covered with well-developed tubercles of two kinds—(*a*) broad and relatively flat, (*b*) narrow and high (nipple-like).

(*a*) The broad tubercles occupy principally that portion of the skin situated along the cranial half of the dorsal fin and between it and the operculum. They secrete a mobile milky fluid which we have not yet had an opportunity to examine critically. An account of this fluid will be given in another paper. [This has since been done.] But the nature of the exudate, its microscopic appearance, and the histological structure of the tubercles lead us to believe that this fluid is toxic. The tubercles consist of a sac opening on the surface by a fine pore more deeply pigmented than the surrounding skin. The histological structure of these broad tubercles is very simple and is shown in Fig. IV.

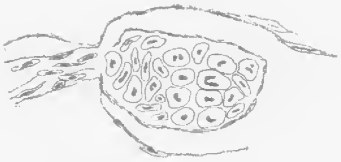
It consists of aggregations of small, almost perfectly circular cells containing one, sometimes two nuclei, in a matrix of dense fibrous (collagenous) tissue. The cell columns lie just outside the lining membrane of the sacs, and in the sacs themselves may be seen small clumps of similar cells, the nuclei of which stain very deeply, while the cytoplasm stains feebly and is almost transparent. These tubercles are true glands; they are contractile and during life



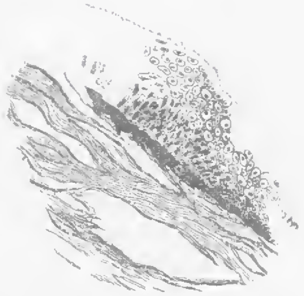
Text-figure 5.—Various aspects of "sense organ."



Text-figure 6.—Section of skin over sense organ.



Text-figure 7.—Section of slime-gland.



Text-figure 8.—Section of skin.

project with considerable force the fluid referred to. After death of the fish pressure on the tubercles produces a similar effect.

(*b*) NARROW HIGH TUBERCLES.—These are arranged in a row along the side of the fish, being definitely connected with each other along their whole length of the row and are associated with the "sense organs" of the skin, which underlie them. The form of the "sense organ" is shown in Fig. V, and the histological structure of the overlying tubercle in Fig. VI. The "sense organ" is tubular along its whole length, but it does not seem to have any directly defensive or offensive function.

SKIN GLANDS.—Casual study of these glands reveals a histological structure shown in Fig. VII. They are particularly abundant over the whole skin, and in structure are similar to the slime glands described and figured by Reed (*loc. cit.*). At the end distal from the surface the cells are large and ovoid, containing either one very large multilobar nucleus or two or more nuclei, which in general stain deeply. Nearer the surface these cells tend to become spherical with a compact rounded nucleus. The lining cells of the duct are flattened and elongated.

As has been noted, these glands are noticeably numerous, which goes perhaps to explain the extraordinarily abundant secretion of slime over the whole fish noticed in all the live or recently dead specimens examined. In every case we found the fish completely covered by a slime so dense that the fish rather resembled a rock completely overgrown by marine flora, and so firmly adherent that heavy hosing was needed to remove it.

Incidentally after removal of this coating of slime the colour of the fish was shown to be rather beautiful—dappled grey and brown in general, with patches of deep violet about the pores of the tubercles over the dorsum, and rich saffron ventrally and especially under the opercular fins. Why the fish conceals this pretty natural appearance in exchange for its slimy coat of dirty blackish green is hard to explain. Reed postulates a nerve stimulus as the cause of this secretion.

Serial sections of the poison gland show the histological structure to be as follows:—

The wall of the gland which is continuous with the stroma consists of tough non-cellular fibrous tissue. In this stroma are numerous alveoli consisting of 3 or 4 lobules, circular in cross-section. The lobules consist of a dense mass of rounded or ovoid cells with a round small central nucleus. The cells are about 10 to 15 μ in diameter, and appear to stain very faintly except during periods of secretory activity. Even then the nucleus stains weakly with hæmatoxylin though the cytoplasm is distinctly eosinophilic. Some sections showed secretion lying in open spaces in the stroma near the spine. This consists of very small cells, about the size of a human red blood cell, which stain very deeply—both nucleus and cytoplasm. In shape the typical cell is either fusiform or flattened and oblong with one or two central nuclei. The basement membrane of the alveoli is simple and consists of stroma modified as to density and direction of fibrils. It apparently contains no pigment.

Elsewhere in general and about the spines in particular the skin has the structure shown in Fig. VIII.

A detailed histological study of the skin glands is reserved for another paper. It is thus evident that the secretion of the skin glands is of two kinds—(*a*) milky white and miscroscopically cellular, (*b*) slimy and non-cellular.

TOXICOLOGY OF THE VENOM OF *SYNANCEJA HORRIDA*.

The results reported are purely qualitative for the reason that, as has been noted before, material for study is scanty, and the strictest economy has necessarily, therefore, had to be practised. These results, however, cannot fail to be convincing, and as more material comes to hand we propose to make our findings strictly quantitative. From Specimen B.L.F/I we obtained something under 2 c.c. of venom in a pure state. From our work we gather that it is not necessary to deal with live specimens. To do so indeed is rather a disadvantage, since handling of the fish irritates it and causes it to discharge its secretion so freely that it cannot be recovered uncontaminated. It appears to us, after considerable experience, to be so difficult to collect completely uncontaminated secretion from all the spines of a fish in the living state, and in the light of our findings in any case so unnecessary, that we now allow to die all live specimens sent to us, and are willing to receive fish of the species dead for 24 or even 48 hours, preserved in sea-water or on ice. In recently dead specimens we make a quick dissection of the spines, stripping away the skin and fascia so as to expose only the spines and poison sacs. All the spines are divided below the sacs with scissors and placed in a small, wide-mouthed test tube. The sacs are then opened carefully and the whole emulsified by mechanical shaking in distilled water. The spines and sac membranes are removed and the whole evaporated. The dried residue is then emulsified in normal saline solution. Whether there is any loss in toxicity of the venom as a result of this procedure we are not able to say, but the material thus prepared with which we worked produced qualitative experimental effects to our complete satisfaction.

Microscopically the emulsion is cellular—containing small, highly refractile, rounded cells with a small central nucleus—in appearance similar to those found in the secretion of the large broad tubercles of the skin. We do not, however, suggest that the secretions are chemically or physiologically identical.

From the original sample of venom studied, we obtained results which are only as yet roughly quantitative. But qualitatively we believe them to be sufficiently striking for record.

The original sample from one fish was so emulsified in normal saline solution as to give a dilution of 1 in 10. This diluted venom was used on laboratory animals as follows:—

GUINEA-PIG I.—0·1 c.c. of the venom emulsion was injected beneath the skin of the abdomen in the right side posteriorly. No exact record of the results was kept except to note that at first the animal was more active than usual, but later became very quiet, refused food. and completely lost the use of both hind limbs. This effect lasted right through the possible period of observation—about 6 hours. Satisfied that the gland secretion had a definite physiological effect, as a preliminary to further work we decided to store the venom on ice, since we wanted to know whether the toxic effect was a stable function or suffered change in keeping. In a busy laboratory this is a matter of some importance.

A week later the venom emulsion was brought to original volume and tested as follows:—

GUINEA-PIG II received 0·2 c.c. subcutaneously, and GUINEA-PIG I, 0·2 c.c. to serve as a control. Beyond a slight increase of activity the control animal showed no response over the period of observation. It had possibly acquired an active immunity. The effects on Guinea-pig II were noted:—

Immediate effect—Increased activity.

5 *minutes*—Slight intermittent convulsive shuddering. (*Note:* This effect is frequently observed in this laboratory in animals which have had to endure relatively prolonged handling.)

10 *minutes*—Continuous marked convulsive shuddering followed by spasmodic contraction of the diaphragm involving stoppage of respiration at every third or fourth respiratory effort. There is spasm of the hind limbs.

15 *minutes*—In forward movement animal can use only fore limbs properly—i.e., it walks with the fore limbs and by a jumping effort draws both hind limbs together towards the body. The hind limbs appear to be paresed.

The respiration rate is decreased.

The animal performs the act of chewing and swallowing continuously. Refuses food and crouches in a corner of its cage.

20 *minutes.*—The hind feet are splayed and spread over a wider base than normal and are extended posteriorly.

25 *minutes*—The intervals between respiratory spasms seem longer. The animal moved once spontaneously in 5 minutes.

40 *minutes*—There is complete paralysis of both hind limbs. On attempting to rise the animal rolls over on its side. It brushes its nose with its fore paws. Respirations are slow and shallow, abdominal respiratory movement being just perceptible. The hind legs are extended and spastic.

50 *minutes*—The fore limbs, especially the right, are paralysed, and both hind limbs markedly so.

The animal is completely unable to rise.

The respiratory excursion is deeper, but slow and still very shallow, respiration being mainly thoracic. The animal lies so that the fore limbs are extended flat along the ground, while the hind part of the animal is twisted so that the hip rests on the ground in the position assumed at the last attempt to rise and walk. The eyes are glazed and staring. The animal does not blink (? abolished corneal reflex).

70 *minutes*—Animal slightly recovered; attempts to walk.

80 *minutes*—Another paralytic spasm, involving chiefly right hind leg and then both hind legs.

2 *hours*—Slight general improvement.

4½ *hours*—Unable to use right hind limb.

6½ *hours*—Condition the same.

8½ *hours*—Paralyses of limbs passed off.

Next day.

12 *hours after last observation*—Animal shows slight but fairly continuous convulsive shuddering; is inactive and refuses food. Survived. Venom stored on ice.

One week later—Guinea-pig III. received 0·2 c.c. subcutaneously. Guinea-pig I. received 0·2 c.c. subcutaneously (control).

Guinea-pig I.	*Guinea-pig III.* This was normally a nervous animal.
15 minutes—Abnormally active 30 minutes—Active, feeding	Ditto.
	Very quiet, crouching. Slight convulsive shudder. Right hind limb drags on walking, though the animal can use the limb for scratching. Though a nervous animal, requires strong stimulus before it will move.
35 minutes—Active, normal	Marked transient paresis of both hind limbs, especially of the right. Brushes imaginary object from its nose. Corneal reflex +. Respirations slow and shallow.
45 minutes—Normal	Respirations very shallow. Corneal reflex sluggish.

60 minutes—Normal	Hind feet splayed. Spastic paralysis of both hind limbs. Corneal reflex sluggish.
70 minutes—Normal	Marked paralysis of both hind limbs.
90 minutes—Convulsive shuddering, still active but rolled over on hips once	0·2 c.c. venom injected. Marked paralysis of diaphragm. Simple reflex reaction time delayed.
1¾ hours—Sluggish, slight intermittent convulsive shuddering, diaphragm retracted at every third inspiration.	As before. Respiratory movement almost imperceptible.
2 hours—Rather sluggish but quite active when stimulated	Animal anæsthetised. See below.
2¼ hours—Fully recovered, feeding.	

Two hours after the start of this experiment, Guinea-pig III. was anæsthetised with open ether while its hind limbs were still in a state of what appeared to us to be one of maximum paralysis for the amount of venom used. The flexor muscles of the leg and the sciatic nerve were quickly exposed, and subjected to a very weak faradic current in an attempt to determine whether the venom acted on the end plates of the motor nerves. From our observations recorded above (necessarily incomplete) we surmised that the action of the venom was, similar to that of cobra venom [Cushny[5]], neurotoxic not myotoxic. Both muscle and nerve, however, gave a response.

The experiment is, however, by no means conclusive, for two reasons: (1) The instrument used was that commonly employed for testing degenerated muscle response in humans. Since the strongest current supplied was just sufficient and all the others insufficient to elicit a response by human muscle, the instrument was tentatively tried on our animals. Possibly even then the current was too strong to elicit differences in response in guinea-pig muscle. (2) The dose of venom was too small to produce effects which could be distinguished from normal responses of nerve or muscle by the apparatus at our disposal.

Both of these factors probably operate, and we are investigating further on these lines, since our experiments leave no room for doubt that the venom is definitely neurotoxic or myotoxic.

We should like to remark here upon the marked abnormal activity of our animals immediately after receiving venom. We interpret this to signify the presence of pain in the animal. We have been careful to exclude any other stimulus which might produce this result, and conclude by analogous observations on other animals that this increased activity is probably due to actual local pain at the site of inoculation.

Hæmotoxic Action of the Venom.

This experiment was only roughly quantitative since our supply of venom was very small. In the first instance we desired to establish only that the venom was hæmotoxic or not. The following series was set up, and the results are recorded in the table below:—

The venom was thoroughly emulsified by shaking in the original dilution of approximately one part of venom to nine parts of 0·85 per cent. saline solution—(Venom A).

This was allowed to settle and the supernatant pipetted off—(Venom B).

A and B were then mixed with a 3 per cent. suspension of guinea-pig red blood cells, thrice washed.

At the same time the protective action of serum was tentatively investigated.

The results are set out in the table below:—

Venom c.c.	Cells 3% c.c.	Serum c.c.	Saline.	Hæmolysis.
A 0.1	0.1	Nil	To 0.3 c.c.	++++
B 0.1	0.1	Nil	To 0.3 c.c.	+++
A 0.1	0.1	Heated 0.04	,,	+
A 0.1	0.1	Heated 0.1	Nil	trace
A 0.1	0.1	Unheated 0.1	,,	—
Control—				
A Nil	0.1	Nil	To 0.3 c.c.	—

Incubated at 37 deg. C. for 1½ hours, and then at R.T.° for 15 hours.

++++ = Complete hæmolysis. +++ = 75 per cent. hæmolysis. ++ = 50 per cent. hæmolysis. + = 25 per cent. hæmolysis. — = 0 per cent. hæmolysis.

It seems also as if the inhibitory substance in normal unheated serum is thermolabile. This aspect of the question, however, requires a lot more investigation. [We have since investigated this problem, and our results will later appear in another place.]

SUMMARY.

1. The myology and anatomy of the dorsal fin spines of *Synanceja horrida* are described.

2. The histology of the poison sacs of the dorsal spines and of certain skin glands is defined.

3. The sacs of the dorsal fin spines are shown to secrete a venomous substance, on the following grounds:—

(*a*) The substance within the sacs exerts a toxic action on the voluntary and involuntary muscles of laboratory animals. Whether this action is neurotoxic or myotoxic has not been definitely determined. It is probably neurotoxic.

(*b*) This substance has a lytic action on the red blood cells of guinea-pigs.

4. The lytic substance of *Synanceja* venom can penetrate red cells independently of the aid of fresh serum.

5. Fresh unheated serum probably inhibits the action wholly or partly of the venom.

6. The inhibitory substance in the serum is probably thermolabile.

7. Recovery from the gross effects of the venom conveys some degree of active immunity.

APPENDIX.

In the course of this research we have found the distribution and size of the poison sacs of *Synanceja horrida* to be variable, as noted in the paper.

Specimen B.L./F.II had no poison sacs at all. In addition, this fish showed a complete absence of the fourth dorsal spine, the skin of the third posteriorly and that of the fifth anteriorly being continuous with the skin of the dorsum generally, and having no direct connection one with the other.

In a fifth specimen just received in this laboratory from Sandgate, the sacs on the first five spines, counting from the cranium, were purely vestigial. They increased in size and venom content up to about the tenth, and from that to the thirteenth were below average size.

Clinical Notes on a Case of Poisoning by Stone Fish Venom.

Supplied by M. J. Gallagher, M.B., Ch.M., Mackay.

"On the evening of 22/2/25 Mr. E.M.B. stood on a 'stone fish' in the Pioneer River, Mackay. The spine of the 'stone fish' entered the sole of his foot midway between the ball of the great toe and that of the little toe. Instantly the pain in the foot was intense, the patient felt nauseous, and upon hopping about two paces to the bank he collapsed and fainted. He recovered sufficiently to drag himself to his house, 100 yards away, when he again fainted. His wife and some friends put him on his bed, where he fainted once more. Upon recovering he was given brandy and his foot was put into a bucket of hot water. His pain was only slightly eased, and as he still felt cold and sick his friends prevailed on him to consult a doctor. About three hours after receiving his injury he was brought into my surgery. He looked pale and ill—cold perspiration about his brow and around his lips; temperature 96·4 deg. F., pulse 110.

"The sole of his foot was swollen in the region of the wound. It was opened up and swabbed with pure carbolic acid and methylated spirit. There was no discolouration of the tissues around the wound. The patient elected to go home, and his friends carried him out to a motor-car, where he fainted. Upon coming round he still desired to go home, where he arrived in due course. Forty-four hours later I saw him at his home and he said he was suffering agony. His foot was enormously swollen and his leg up to the knee was intensely swollen, red, shining, and tender. (Temperature 102·4 deg. F., pulse 108, respirations 26.) He was taken immediately to hospital, where hot baths alternated with ichthyol foments to his leg for forty-eight hours; then under general anæsthesia multiple incisions were made in the cellulitis of his foot and leg. The whole of the skin and subcutaneous tissues of the foot and leg, in its whole circumference as far as the knee, formed but the outer wall of a bag of pus, the inner wall being formed by the deep fascia covering the muscles and bones.

"He improved progressively every day both in his general condition and leg condition, and all went merry as a marriage bell until 10.30 a.m. on 7/3/25 (fourteen days after injury), when, without warning, he felt as though a boa-constrictor had suddenly thrown its coils around his waist and was squeezing the breath out of him. The pain was most intense—his words were 'frightfully unbearable'—and appeared to be in the epigastrium, as though all his viscera had been tied in a knot and the knot gradually tightened.

"He had increasing difficulty in breathing, until finally he felt his breathing stop completely and he lost consciousness. Just before losing consciousness he had pressed his bell, and when the nurse arrived she found him unconscious, cyanosed, saturated with perspiration, and gasping for breath.

"Artificial respiration soon restored him to consciousness, and with great difficulty he was able to whisper—'Can't breathe—terrible pain in stomach.'

"Mustard plaster to epigastrium, H.I. morphine gr. ¼, atropine gr. 1/150, tetanus antitoxin 6000 units intrathecally, 15000 units subcutaneously.

"No further spasm occurred, but stiffness and soreness around epigastric region lasted for about four days after attacks, and during a period of eighteen months from time of seizure. He had four periods during which he felt a tightness in the epigastrium and had slight difficulty in breathing. He has been free from these attacks for the last six months (up to February 1928).

"On 28/3/25 skin-grafted a large denuded area which had sloughed out over the instep.

"The patient was totally incapacitated for over four months. He is now (February 1928) quite well, and has only slight limitation of extension of his ankle, but it is insufficient to cause him any real disability."

[NOTE.—Dr. Gallagher's vivid narrative would have been a striking confirmation of our findings had he not raised the question of the respiratory failure being due to tetanus. So keen an observer as Dr. Gallagher shows himself to be would not have failed to observe spasm of other muscle groups, which I think would undoubtedly have occurred as a result of tetanus toxin. Also, I do not think tetanic symptoms would have subsided so rapidly even after such large doses of antitoxin. Diaphragmatic spasm alone is a constant symptom of poisoning by animal venoms, though it is undoubtedly difficult to explain the obviously late development of this effect in this case. In our laboratory animals it is one of the earliest effects, but it passes off relatively quickly, as our experiments show.

On the whole, however, I am inclined to attribute this striking effect to the *Synanceja* venom. Though Dr. Gallagher's observations tend to confirm our findings and those of other workers on snake venoms, and though that fact affords us some little satisfaction, we cannot but regret the terrible and unfortunate fact which preceded that confirmation.]

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